REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

In the specification, paragraphs have been amended to insert sequence identifiers. A sequence listing containing the sequences disclosed in the specification is also submitted.

Claim 4 is requested to be canceled without prejudice or disclaimer thereto. Claims 1 and 26 are currently being amended to recite that the at least two administrations are from 2 to 6 days apart and to limit the scope to the elected group. Support for this limitation can be found, *inter alia*, in pargraph [0023] of the published application and in original claim 4. Claim 14 has been amended solely for clarity.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-3 and 5-28 are now pending in this application, of which claim 28 is withdrawn.

I. Objections to the Specification

The Examiner has objected to the specification for failing to comply with 37 C.F.R. § 1.821(a)(1) and (a)(2). Applicants submit herewith a Substitute Sequence Listing and appropriate amendments to the specification to include sequence identifiers. This sequence listing is identical to that filed in the PCT application and does not constitute new matter.

II. Priority

The Examiner alleged that the parent U.S. Appl. Nos. 60/510,086; 60/526,517 and 60/567,771 do not disclose the presently claimed invention. In fact, the Examiner points to one embodiment disclosed therein as allegedly teaching away from the present invention. Applicants strongly disagree.

U.S. Appl. Nos. 60/526,517 and 60/567,771 both state "In one embodiment NOI, or another product which may stimulate an immune response (such as a polypeptide antigen), is not administered to the subject at least 7 days, such as at least 14 days or at least 28 days after the last administration of NOI in any of the administration regimens mentioned herein." See page 6, lines 18-21 of both specifications. Therefore, they both disclose regimens falling within the range presently claimed. Further, U.S. Appl. No. 60/510,086, while not making this explicit statement, shows immunization clusters that are 28 days apart in Example 6. Thus, all three applications support intervals within the claimed 21-365 day range. Merely teaching an alternative embodiment does not constitute "teaching away" from the present invention, especially in light of the support for the present invention provided by those priority applications.

In view of this support in the priority applications, Applicants respectfully request that the priority date of the present invention be properly accorded at least the filing date of the first priority application, October 10, 2003.

III. Claim Objections

The Examiner has objected to claim 1 for encompassing a non-elected invention. Claims 1 and 26 have been amended to recite that the second immunization comprises at least one administration of a protein comprising the T cell epitope, thus limiting the claims to the scope of the elected invention. Accordingly, Applicants respectfully request that the objection be withdrawn.

IV. Claim Rejections Under 35 U.S.C. § 112, second paragraph

Claim 14 is rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the inventinon. Specifically, the Examiner asserts that claim 14 is vague for reciting "or" in line 4 and "and" in line 5. Applicants respectfully traverse this rejection.

Without acquiescing to the rejection and solely to advance prosecution, claim 14 has been amended to more clearly recite the compositions in the alternative as a Markush group. As the claim is unambiguous, Applicants respectfully request that the rejection be withdrawn.

V. Claim Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-14, 18-21, 26 and 27 are rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the enablement requirement. Specifically, the Examiner asserts that undue experimentation would be required to make and use the claimed invention because the specification allegedly fails to disclose working examples of the present invention and that the art is unpredictable. Applicants respectfully traverse this rejection.

The instant application states that the administrations of the first immunizations are preferably 2-6 days apart in paragraph [0023] and goes on to describe the additional facets of the present invention in detail in subsequent paragraphs. Further, the specification provides detailed disclosure on the types of NOI to be used (*see, e.g.,* paragraphs [0051]-[0087], [0102]-0109], [0193]-[0196]) as well as the protein to be used (*see, e.g.,* paragraph [00110]) and administration techniques (*see, e.g.,* paragraphs [0111]-[0128]). Dosages, which may be varied according to antigen type and desired effect, are described in , *inter alia*, paragraphs [0135]-[0137]). Assays for determining the effectiveness of the present methods are provided in at least paragraphs [0150]-[0158].

In addition to this disclosure, examples are provided utilizing these methods. Several NOIs, the proteins, and assays are provided in detail as part of working examples in paragraphs [0197]-[0224], with the results described in the examples and figures. Example 3 describes immunization with plasmids encoding different epitopes. Immune responses, measured by CD8 ELISPOTS, peaked when the administrations were given within four days (Figs. 3A and 3C) or six days (Fig. 3B). Example 4 confirms this optimal administration time frame, as shown in Fig. 4. Further, Example 5 discloses that repeat administration of the NOI within a 48 hour time frame enhances humoral immune response (Fig. 5). Example 6 describes vaccinating pigs with two rounds of immunizations, each consisting of four administrations of a NOI. These two immunizations were spaced 28 days apart and induced significant cellular immune responses. Thus, the examples disclose that repeat administrations of NOI enhances the immune response generated against the encoded antigen, and that boosting within the time frame presently claimed further increases the immune response.

Indeed, Examples 13-17 compare the "clustered" administration method over 4 days versus conventional methods and consistently found that the present invention provides greater immunity. This surprising effect was repeated with different antigens, different animal models and different experiments, all with enhanced immune responses generated, as measured by several different assays. Thus, the examples of the present invention provide numerous working examples of inducing enhanced immune responses when the first immunization has repeat administrations within the claimed 2-6 day interval.

Boosting with a second immunization with protein is described in paragraphs [0026] and [0109] and [0110]. While no working example is provided using this type of second immunization, Applicants remind the Examiner that, as reiterated in M.P.E.P. § 2164.02, the courts have held that compliance with the enablement requirement does not turn on whether an example is disclosed. Indeed, an applicant need not have actually reduced the invention to practice prior to filing. *See Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987). In summary, the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *See In re Borkowski*, 422 F.2d 904, 908 (CCPA 1970).

Here, the Examiner points to various references as teaching that the exact regimen for DNA prime/protein boost is variable, and even questions why a different boost time frame is claimed than that disclosed in the art. The present examples show that later second immunizations provide strong immunity, albeit with DNA. Those skilled in the art reading the instant specification would have understood that a second immunization could be done using any suitable T cell epitope. The present invention should not be limited to exact conditions disclosed in the Examples when optimizing conditions within the scope of the claimed invention would have been routine for one skilled in the art. Those skilled in the art had what they needed to practice the claimed invention upon reading the present specification and methods disclosed therein.

The Federal Circuit has consistently held that "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (citations omitted). Indeed, the fact that experimentation may be complex does not

necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, (Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737. Further, the Patent Office specifically states

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art.

M.P.E.P. § 2164.08(b)(internal citations omitted).

Here, although the exact conditions may be optimized for maximum effectiveness, a person of skill in the art would readily be able to perform such optimization using routine methods as provided in the present specification. For example, the exact intervals used for the first and second immunizations could be determined using the immunization protocols provided in the examples. Dosages of the NOI and protein can be adjusted according to the variables provided in the specification, as well as observed outcomes during optimization. The specification provides the key elements for consideration and framework for adjusting the claimed method according to the specific T cell epitope to be used. Such optimization is routine for one of skill in the art and is therefore not undue.

In sum, the present specification shows that the administrations required by the first immunization as claimed induces an enhanced immune response and describes methods for optimizing the second immunization. As one of skill in the art would be able to make and use the claimed invention, the specification enables the present claims. Accordingly, Applicants respectfully request that the rejection be withdrawn.

VI. Claim Rejections Under 35 U.S.C. § 102

Claims 1-5, 8, 9, 11, 14, 18-20, 26 and 27 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Billaut-Mulot *et al., Vaccine* (2001) 19:95-102. Specifically, the Examiner asserts that this reference teaches a method of eliciting a T cell response against

HIV viral infection in a mammalian host comprising intradermal administration of a Nef-encoding plasmid over three weeks followed 14 weeks later by a boost with Nef protein. Applicants respectfully traverse this rejection.

An anticipation rejection under 35 U.S.C. § 102 requires a showing that each limitation of a claim is found in a single reference, practice or device. *See In re Donohue*, 766 F.2d 531 (Fed. Cir. 1985). In order for a reference to be anticipatory, it must "be enabling and describe the applicant's claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." *See In re Paulsen*, 30 F.3d 1475 (Fed. Cir. 1994). Applicants assert that the cited references do not anticipate the present claims as they do not teach each and every element of the claims.

Billaut-Mulot teaches successive administrations of a Nef-encoding plasmid over three weeks followed 14 weeks later by a boost with Nef protein. Page 96, right hand column, first paragraph. In contrast, the present invention requires that the first immunization comprise at least two administrations of a NOI from between 2 and 6 days apart, a shorter time frame than that taught by the cited reference. Further, claim 2 requires that all administration of the NOI occur between 2 and 6 days, whereas Billaut-Mulot teaches administering the plasmid over three weeks. Indeed, as discussed above and shown in the examples of the present application, the shorter time frame of administration as claimed generates an enhanced immune response. Therefore, as the cited reference does not teach each limitation of the present claims, it cannot anticipate the present invention. Applicants respectfully request that the rejection be withdrawn

VII. Claim Rejections Under 35 U.S.C. § 103

Claims 1-14, 18-21, 26 and 27 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Doria-Rose *et al., Methods* (2003) 31:207-216 in view of Berglund *et al., Vaccine* (1999) 17:497-507 and Horvath *et al. Immunol. Letters* (1998) 60:127-136. Specifically, the Examiner applies Doria-Rose for teaching DNA vaccination followed by a protein boost and further applies the secondary references to teach methods for inducing an immune response against influenza by administering a nucleotide encoding influenza antigens or administering the influenza-derived peptide. Applicants respectfully traverse this rejection.

The Supreme Court has recently reaffirmed the *Graham* factors for the determination of obviousness. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727,1739 (2007) 127 S. Ct. 1727 (2007) (holding that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions). These four factual inquiries under *Graham* are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the prior art and the claims in issue; 3) resolving the level of ordinary skill in the prior art; and 4) evaluating evidence of secondary consideration. *Graham v. John Deere*, 383 U.S. 17-18 (1966). In accordance with these factors, to establish a *prima facie* obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Applicants assert that this burden has not been met.

Doria-Rose teaches that combination vaccines using DNA administrations followed by boosting with DNA or protein may be used to induce an immune response. However, the time frames taught and recommended in this reference exceed those presently claimed. For instance, Table 2 of Doria-Rose teaches that DNA should be given in doses spanning weeks. The second dose of DNA is given either 4 or 8 weeks after the first, the third dose is given at week 25, and protein or DNA is given at weeks 50 and 73. Further, Figure 1 of this reference summarizes another experiment in which DNA was administered at 8 week intervals, without protein administration. Throughout this reference, the authors refer to administrations over several weeks, and no shorter time intervals are discussed or even suggested. Therefore, Doria-Rose teaches much longer intervals between administrations than presently claimed.

This difference in administration intervals between Doria-Rose and the claimed invention is not trivial, as the examples of the present invention show an enhanced immune response when administered 2, 4 or 6 days apart, as discussed above. For example, Fig. 3 shows an enhanced immune response when the NOI is administered at 4 day or 6 day intervals. Examples 13-17 compare 4 day administrations with conventional administration schedules and found the clustered administrations to be more effective. As the art had previously relied upon longer intervals, presumably to allow maximal immune responses, the shorter interval as claimed is surprising and therefore nonobvious.

The secondary references do not remedy this deficiency as neither teach a first immunization with at least two administrations of a NOI encoding the T cell epitope over 2-6 days, followed by a second immunization with a protein comprising the T cell epitope. Berglund teaches immunizing mice with Semliki Forest Virus encoding LacZ or NP, followed by a second immunization with the same virus two weeks later. *See* Results, section 3.1 beginning on page 499 and section 3.3 beginning on page 501. Thus, neither immunization with NOI followed by a protein, nor the time frames for administration is taught or suggested by Berglund.

Likewise, Horvath merely discloses administration of the HA peptide in a single dose. Neither Doria-Rose, Berglund nor Horvath teach or suggest first immunization with a NOI comprises at least two administrations of a NOI encoding the T cell epitope over 2-6 days, followed by a second immunization with a protein comprising the T cell epitope. To the extent that any reference may teach the administration of nucleotide followed by a protein, they teach that the nucleotide should be administered at intervals much longer than those presently claimed. Because none of the references, alone or in combination, teach or suggest the present invention, they cannot render the present invention obvious. Accordingly, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect

information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date Nov. 21, 2008

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